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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/050,249	03/30/98	OKAMURA	H OKAMURA=2B

HM12/1006

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EXAMINER	
FITZGERALD,D	
ART UNIT	**PAPER NUMBER**
1646	10

DATE MAILED: 10/06/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

PTO-90C (Rev. 2/95)

1- File Copy

Office Action Summary

Application No.	Applicant(s)
09/050,249	OKAMURA, et al.
Examiner	**Group Art Unit**
David L. FITZGERALD	1646

☒ Responsive to communication(s) filed on *18 June 1999 (supp. prelim. amdt.)*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *THREE (3)* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *56 and 59-88* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *56 and 59-88* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☒ received in Application No. (Series Code/Serial Number) *08/502,535*.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *ed with ap*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. Receipt is acknowledged of the preliminary amendments filed 30 March 1998, 15 May 1998, 15 October 1998, 21 October 1998, 27 May 1999, and 18 June 1999.

2. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. IGIF-specific antibodies (classified, *e.g.*, in Class 530/subclass 388.23) and analytical (435/7.1), immunoaffinity (530/413), and IGIF-inhibitory (424/145.1) methods employing them, upon which claims 23, 24, 26, 28, 29, 32, 35, 41-43, 45-47, 49-52, and 56-58 previously presented for examination read.

II. IGIF polypeptides (530/351) and compositions containing them (424/85.2), upon which claims 36-40, 44, 48, and 53-55 previously presented for examination read.

Although the polypeptides and antibodies are related, the products are materially and functionally dissimilar, and the antibodies may be made without resort to the proteins *per se*, *e.g.*, by immunizing against immunogenic peptides or conjugates. The inventions are therefore patentably distinct, each from the other. They have acquired separate status in the art, as shown by their different classifications and because they would entail divergent searches of the research literature and consideration of unique issues of patentability. Restriction for examination purposes as indicated is accordingly proper.

During a telephone conversation on 26 May 1999, Allen Yun made a provisional election without traverse to prosecute the invention of group I as set forth above, and the submission of a new claim set in the amendment filed 18 June 1999 is construed as an affirmation of that election. Applicant is reminded that if the cancellation of the claims to the non-elected invention has caused one or more of the currently named inventors to no longer be an inventor of at least one claim remaining in the application, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b). Any amendment of inventorship must be accompanied by a petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(i).

3. New claims 59-88 are the result of a series of telephone conversations between the undersigned and applicant's representative, Allen Yun, held in May and June of 1999, which this paper serves to summarize. Approaches to securing claims of some breadth were discussed. The examiner drafted a set of claims which he considered to be free of any concerns relating to 35 U.S.C. § 112, and he provided the draft by fax to Mr. Yun on 3 June 1999. The new claims presented by preliminary amendment (with the exception of the point discussed ~~above~~ below in

connection with the rejection under 35 U.S.C. § 112, second paragraph) are identical to the examiner's draft claims.

In response to concerns expressed by Mr. Yun during the noted telephone conversations, the examiner notes particularly that the "specific" binding required by the claims should be construed in its broader sense not to preclude cross-reactivity. That is, the antibodies of the claims are "specific" for murine IGIFs inasmuch as they are the antibodies that would be obtained against a mIGIF immunogen according to conventional methodology employed in the art, but some such antibodies could also bind other proteins, *e.g.*, structurally related IGIF species homologs. (Indeed, a narrower construction requiring that the antibodies bind to mIGIF and to no other proteins would not be supported by the disclosure as filed.)

The examiner recalled that in the prosecution of parent application serial no. 08/502,535, also examined by the undersigned, art rejections directed to polypeptide and antibody claims were lodged based on the disclosure in the prior art of a 55-70 kDa IFN-γ-inducing factor purified from mouse serum, in which the murine IGIF polypeptide of the present invention is inherently present as a component. *See* Nakamura *et al.* (*Infect. Immun.*, 1993), describing the 55 kDa protein and its biological activity, and Okamura *et al.* (*Infect. Immun.*, 1995), which evidences that the 18 kDa IGIF is present as a component of the 55 kDa material described in the prior art. The examiner also recalled that counsel, Mr. Browdy, had traversed a requirement for restriction between the "protein" and "antibody" claims in part by conceding that given the protein, a monoclonal antibody specific for the protein would have been obvious in view of it.

Notwithstanding the disclosure in the prior art of a complex comprising the instant mIGIF and Mr. Browdy's concession, the examiner considered that in view of the present level of knowledge in the art concerning the useful properties of IL-18, a plausible rationale for the nonobviousness of the instant claims could be argued, provided however that Mr. Browdy's concession could be construed as relating to *prima facie* obviousness rather than to an ultimate legal conclusion of obviousness. After reviewing the record of the '535 application,[1] the

[1] The examiner extends his thanks to Mr. Yun for kindly providing the examiner a courtesy copy of the reply filed 14 February 1997 as well as copies of the Nakamura and Okamura references.

examiner is constrained to conclude that Mr. Browdy's concession related unambiguously to the ultimate legal conclusion of obviousness, *viz.*, that given the protein of claim 1 in the prior art, a monoclonal antibody specific for it is obvious under 35 U.S.C. § 103 as a matter of law. Art rejections directed against certain of the claims are therefore set forth below.

4. The following sets forth the basis of the nonstatutory double patenting rejection.

The nonstatutory double patenting rejection, whether of the obvious-type or non-obvious type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 U.S.P.Q. 644 (C.C.P.A. 1969); *In re Vogel*, 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970); *In re Van Omum,* 686 F.2d 937, 214 U.S.P.Q. 761 (C.C.P.A. 1982); *In re Longi,* 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985); and *In re Goodman,* 29 U.S.P.Q.2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

A registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

5. Claims 69-80, 83, 84, and 88 are rejected under the judicially approved doctrine of nonstatutory double patenting as being unpatentable over claim 2 of U.S. Patent No. 5,912,324. Although the conflicting claims are not identical, they are not patentably distinct from each other because they encompass common subject matter and/or obvious variations thereof.

Claim 2 of the '324 patent is directed to a method of recovering a murine IGIF protein by column immunoaffinity chromatography using a specific monoclonal antibody. It is thus subgeneric to instant claims 74-80 and 84. The claim is furthermore not patentably distinct from instant claims 69-73, 83, and 88, directed to immunodetection methods, because the methods all exploit the distinguishing novel characteristics of the antibodies they employ, *viz.*, the ability to specifically bind an IGIF. Moreover, the claims differ only with respect to steps involving conventional manipulations routinely practiced in the art for immunopurification or immunodetection methods generally. The latter claims are therefore directed to subject matter which the skilled artisan would reasonably expect to be able to practice without limitation upon the expiration of the '324 patent. Lastly, the subject matter of all of claims 69-80, 83, 84, and 88 is fully supported in the '324 patent, issued on the parent of the instant application, and all of such claims could have been presented in the application which matured to that patent. A grant of

patent on the instant claims would therefore vest a proprietary interest in the subject matter of the '324 patent and subject matter not patentably distinct therefrom in a second patent. *Compare In re Schneller*, 397 F.2d 350, 158 U.S.P.Q. 210 (C.C.P.A. 1968); *In re Berg*, 140 F.3d 1428, 46 U.S.P.Q.2d 1226 (Fed. Cir. 1998).

6. Claims 59-67, 69-72, and 74-80 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 59 and the claims dependent therefrom are vague and indefinite because it is not clear whether the use of the past-tense "hybridized" requires the actual practice of a hybridization step as a component of or preliminary to the method. Amendment of claim 59 to recite "hybridizes," thus to convey only the capability of functioning according to the recited limitation, will clarify the claims in this regard.

7. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 56 and 59-88 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nakamura *et al.* (*Infect. Immun.* 61: 64-70, 1993) in light of counsel's concessions made during the prosecution of parent application serial no. 08/502,535, now U.S. Patent No. 5,912,324.

Nakamura describes a purified IL-12-like factor (abstract) which migrates at 70-75 kDa on gel filtration and at 50-55 kDa on SDS-PAGE (page 68, col. 2, second paragraph). Compositions comprising this factor and various other substances in PBS (page 65, paragraph bridging columns) induce the production of IFN-γ in resting T and NK cells (abstract).

In the reply filed 14 February 1997 in the '535 application, counsel stated the following in traversal of a requirement for restriction between, *inter alia*, original claims 1 and 18:

> Applicant hereby concedes that, if the protein of [original] claim 1 were available to the prior art (which includes knowledge of its biological activity as set forth in the claim), it would be obvious, within the meaning of 35 U.S.C. § 103, for one of ordinary skill in the art to make a monoclonal antibody which is specific to such protein.

Original claim 1 reads as follows:

> 1. A protein having the following physicochemical properties:
>
> (1) Molecular weight
> 19,000 ± 5000 daltons on gel filtration and sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE);
>
> (2) Isoelectric point (pI)
> 4.8 ± 1.0 on chromatofocusing;
>
> (3) Partial amino acid sequence
> Possessing partial amino acid sequences in SEQ ID NOs: 1 and 2; and
>
> (4) Biological activity
> Inducing the interferon-γ production by immunocompetent cells.

Although Nakamura teaches that the factor it describes is apparently homogeneous and has a molecular weight outside of the range specified in claim 1, the prior art factor appears to meet the limitations of claim 1 for the following reasons. As evidenced by Okamura *et al.* (*Infect. Immun.* 63: 3966-3972, 1995), which lists several authors in common with the Nakamura reference, an 18-19 kDa IFN-γ inducing factor is a component of the 70-75 kDa factor known in the prior art. Okamura teaches (paragraph bridging pages 3970-71):

> This factor was purified from [a murine] liver extract . . . . Its isoelectric point determined by Mono P column chromatography was 4.8 . . . . Unexpectedly, the IGIF that was previously found in the sera of mice and that caused endotoxic shock ([citation to the Nakamura paper and an earlier publication]) was shown to contain the same molecule as was purified from the liver extract (Fig. 5). . . . [T]he molecular form of IGIF in serum remains unknown. It may exist in an oligomeric form or may be bound to another molecule.

Additionally, a later paper from the same laboratory (Ushio *et al., J. Immunol.* 156: 4274-4279, 1996) evidences that the 18-19 kDa murine factor described by in the Okamura paper has an amino acid sequence (Fig. 2) which is identical to that shown in instant SEQ ID NO: 2. In view of the similar sources and the identity of structural, biophysical, and functional properties of the

instantly claimed protein and the 18-19 kDa factor described in the Okamura and Ushio papers, it reasonably appears that they are the same.

The only arguable difference between Nakamura and original claim 1 to be addressed is the molecular weight. The 18-19 kDa molecular weight is, however, an inherent property of the IGIF gene product, as evidenced by Okamura and Ushio. The limitations of the claim, moreover, are met if the recited product is identified in the prior art; it does not require that the 19 kDa factor be homogeneous or otherwise purified. Because the characteristic biological properties of mIGIF are identified in the prior art, the prior art complex inherently meets the limitations of the claim insofar as it comprises a discrete 18-19 kDa component.

Nakamura additionally provides evidence which the ordinarily skilled artisan would have interpreted to convey the existence of a factor having the activities described and a molecular weight of *ca.* 21-22 kDa. Fig. 2 at page 67 depicts the electrophoretic separation of the IGIF activity described in the paper; the activity profile is aligned with the pictures of the gel lanes marked a, b, c, and d. Notwithstanding the description in the text of a molecular weight on SDS-PAGE of 55 kDa, the active fraction identified in the figure quite clearly aligns between the 21 and 23 kDa molecular weight markers in lane d. This evidence indicates that Nakamura thus in fact describes a factor inherently having all of the physicochemical properties required by claim 1 and it fully describes the biological activity required as a limitation of the claim.

Because Nakamura describes the protein of original claim 1, including its biological activity, a monoclonal antibody specific for that protein is obvious under 35 U.S.C. § 103 as a matter of law, per counsel's express concession.

To the extent that Nakamura is ambiguous as to the molecular weight and to the extent that claim 1 cannot be fairly construed to read on a material which is said to exhibit a molecular weight outside the recited range, counsel's concession nonetheless weighs in favor of the conclusion that the genus of monoclonal antibodies specific for the Nakamura IGIF material is obvious under § 103. In addition to conceding the obviousness of a mAb to "the protein of claim 1," counsel stated in the reply of 14 February 1997 that "[t]echniques of raising monoclonal antibodies are well known" and that "[k]nowing the biological activity of such protein [as the protein of claim 1], one of ordinary skill in the art would have been motivated to make a

monoclonal antibody for the purpose of immunoaffinity chromatography or for the purpose of blocking its activity. The techniques for doing so are well known." These concessions are generic in nature.

Because the 18-19 kDa IGIF is at the least a significant component of the 55/75 kDa material described by Nakamura (Okamura considers the possibility that Nakamura observed a multimer), a significant number of the antibodies within the genus conceded to be obvious in view of it would have recognized epitopes on the 18-19 kDa component. Furthermore, the prior art teaches the biological activity which counsel has conceded that it would have been obvious to block using a conventionally made monoclonal antibody, and the evidence of record indicates that the biological activity is associated with the 18-19 kDa component of the prior art material. It is therefore the examiner's determination that counsel has conceded the obviousness of the genus of monoclonal antibodies specific for the Nakamura IGIF and has further conceded that it would have been obvious to select from that genus the subgenus of antibodies capable of blocking the activity described in the prior art. Because the evidence of record indicates that such antibodies would meet all of the limitations of the instant claims, such claims are consequently unpatentable under 35 U.S.C. § 103.

The monoclonal antibodies conceded to be obvious, as discussed above, meet the limitations of claims 59, 60, 81, and 86, the latter claim notwithstanding the recited method of making. Because counsel has conceded that it would have been obvious to make a mAb for the purpose of immunoaffinity chromatography or for the purpose of blocking [an IGIF protein's] activity," the mAbs of claims 63, 82, and 87, and the corresponding methods of using them, to which claims 56, 67, 68, 74, 75, 84, and 88 are directed, have been conceded to be obvious. Because the only technique for making monoclonal antibodies known in the art (prior to having in hand a cDNA encoding one) necessarily involves the production of hybridomas and their cultivation to produce and recover the mAbs, the subject matter of claims 64, and 65 has equivalently been conceded to be obvious.

The subgenus of antibodies claimed in claim 61 does not patentably distinguish over the mAb of claim 59 because, as was appreciated in the art at the time of the invention, the great majority of hybridomas obtained in a conventional fusion elaborate IgG or IgM antibodies.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to label an IGIF-neutralizing mAb with an label conventionally known in the art, *e.g.*, an enzyme for an ELISA assay, because the artisan would have expected that the easily detectable mAb would be useful for detecting and quantitating the material for which it is specific. For essentially similar reasons, it would have been obvious to use such an antibody to detect or quantitate a protein having IGIF activity, such as the material described by Nakamura, because the artisan would have found it desirable to be able to do so, *e.g.*, to track the progress of a purification protocol. It further would have been obvious to do so in any format commonly employed in the art, such as ELISA, because the artisan would have expected to realize the recognized advantages of using such formats.

In producing a monoclonal antibody by conventional methodology, it would have been obvious to recover the antibody from a hybridoma culture using any conventional protein purification or manipulation techniques, such as affinity chromatography using an Ig-specific reagent (Protein A and the like) because such techniques were conventionally employed in the art at the time of the invention for the recovery of mAbs and were recognized to be advantageous for producing pure, concentrated immunological reagents.

In using the mAbs for immunoaffinity purification, it would have been obvious to purify a material having IGIF activity, such as the protein described by Nakamura, in a column chromatography format because that format was recognized in the art at the time of the invention as an efficient means for resolving and recovering proteins in immunoaffinity experiments. The artisan would have expected to recover an IGIF material having very high purity and with essentially complete recovery of activity because most biologically active proteins purified by immunoaffinity chromatography prior to the time of the invention could be so recovered following routine experimentation to ascertain effective parameters for the purification steps.

The polyclonal antibody of claim 85 does not patentably define over the monoclonal antibodies conceded to be obvious because, as was appreciated in the art at the time of the invention, the immunization procedure employed to provoke an immune response in a mouse necessarily elicits plural antibody-producing clones in the animal, and it was conventional in the art to follow the progress of the immune response by sampling the animal's serum. Serum from

an immunized animal having a detectable quantity of antigen-reactive antibodies is, by definition, a polyclonal antibody preparation. The artisan would reasonably have expected that antiserum from an animal elaborating mAbs having certain functional properties would exhibit the same functional properties.

In summary, subject matter embraced by each of the claims has been conceded to be obvious as a matter of law or would have been *prima facie* obvious as not patentably defining over the subject matter conceded to be obvious.

9. No claim is allowed. As in the case of claim 2 of the '324 patent, the immunoaffinity and immunodetection method claims would be patentable if amended to require the recovery or detection of a protein having a molecular weight of 19 ± 5 kDa.

10. Any inquiry concerning this communication should be directed to David Fitzgerald, who can be reached by any of the following means:

Telephone	(703) 308-3934
Fax	
All formal papers	(703)308-4242
Informal communications	(703) 308-0294
e-mail (note PTO policies below)	david.fitzgerald@uspto.gov

Inquiries of a general nature should be directed to the Technology Center 1600 receptionists at (703) 308-0196.

DAVID L. FITZGERALD
PRIMARY EXAMINER
ART UNIT 1646

1 October 1999

The best time to reach **Examiner Fitzgerald** is from 9 a.m. to 4 p.m. (Eastern). If he cannot take a call, a message may be left on his voicemail. Should attempts to reach him be unsuccessful, the acting supervisor for this Art Unit, Paula Hutzell, may be reached at (703) 308-4310.

Most official papers and all informal **communications may be submitted to the PTO by fax.** For specific policies, refer to 37 C.F.R. § 1.6 and the notice published at 1096 O.G. 30. To facilitate their receipt and handling, please —

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- **Do not send a duplicate copy** by mail or courier.

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